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09/823,181	03/30/2001	Jingyue Ju	0575/62948/JPW/ADM/BJA	9161

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EXAMINER	
CHAKRABARTI, ARUN K	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 07/01/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/823,181	Ju et al.
Examiner	**Art Unit**
Arun Chakrabarti	1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jun 4, 2003*.

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *74-92* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *74-92* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Detailed Action*

DETAILED ACTION

Double Patenting

1. Claims 74-92 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-22 of U.S. Patent No. 6,046,005 in view of Arbo et al. (International Journal of Peptide and Protein Research, (1993), Vol. 42, pages 138-154) further in view of Liu et al. (Anal. Chem. (2000), Vol. 72, pages 33030-3310).

Claims 1-22 of U.S. Patent No. 6,046,005 disclose basically and fundamentally the same method of instant claims 74-92, for sequencing DNA by detecting the identity of a dideoxynucleotide incorporated at the 3' end of a DNA sequencing fragment using mass spectrometry. The basic steps of detection of DNA of instant claims are same as claims 1-22 of U.S. Patent No. 6,046,005, which comprises a) attaching a chemical moiety via a linker to a dideoxynucleotide, b) terminating a DNA sequencing reaction with the labeled dideoxynucleotide, c) capturing the labeled DNA sequencing fragment on a solid surface, d) washing the surface, e) freeing the DNA sequencing fragment from the surface, and f) analyzing the fragment using mass spectrometry so as to sequence the DNA.

Claims 1-22 of U.S. Patent No. 6,046,005 do not teach a method, wherein the cleavable linkers are a derivative of 4-aminomethyl benzoic acid containing fluorine of claim 74.

Arbo et al teach method, wherein the cleavable linkers are a derivative of 4-aminomethyl benzoic acid containing fluorine of claim 74 (Abstract and page 149, Column 2 to page 151, Column 1).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the chemically equivalent cleavable linkers, which are a derivative of 4-aminomethyl benzoic acid containing fluorine of Arbo et al in the method of claims 1-22 of U.S. Patent No. 6,046,005, since U.S. Patent No. 6,046,005 states, "In such linkers, the linker will comprise a cleavable moiety that is either photo or chemically cleavable (Column 7, lines 1-3)." By employing scientific reasoning, an ordinary practitioner would have been motivated to combine and substitute the chemically equivalent cleavable linkers, which are a derivative of 4-aminomethyl benzoic acid containing fluorine of Arbo et al in the claims 1-22 of U.S. Patent No. 6,046,005, in order to achieve the express advantages, as noted by U.S. Patent No. 6,046,005, of linkers which will comprise a cleavable moiety that is either photo or chemically cleavable.

U.S. Patent No. 6,046,005 in view of Arbo et al do not teach the method, wherein the contacting is performed in a system comprising (I) a channel whose surface is coated with a compound that specifically interacts with the chemical moiety, wherein the channel comprises a plurality of ends, (ii) a plurality of wells each suitable for holding a sample, (iii) a connection between each end of the channel and a well, and (iv) a means for moving the sample through the channel between wells.

Liu et al. teaches the method, wherein the contacting is performed in a system comprising (I) a channel whose surface is coated with a compound that specifically interacts with the chemical moiety, wherein the channel comprises a plurality of ends, (ii) a plurality of wells each suitable for holding a sample, (iii) a connection between each end of the channel and a well, and (iv) a means for moving the sample through the channel between wells (Abstract and Figures 1-3 and Experimental Section).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the method, wherein the contacting is performed in a system comprising (I) a channel whose surface is coated with a compound that specifically interacts with the chemical moiety, wherein the channel comprises a plurality of ends, (ii) a plurality of wells each suitable for holding a sample, (iii) a connection between each end of the channel and a well, and (iv) a means for moving the sample through the channel between wells of Liu et al in the method of claims 1-22 of U.S. Patent No. 6,046,005 in view of Arbo et al., since Liu et al. states, "Considering the wide acceptance of the microtiter well plate format in automated analysis and the potentially low cost of plastic devices, a disposable device equipped with an independent electrospray exit port for each sample well represents an attractive alternative to FIA (Page 3304, Column 1, lines 6-10)." Liu et al provides further motivation as Liu et al. states, "Nevertheless, the model application demonstrates the potential of automated analysis with the present device design (Page 3309, Column 1, last sentence of the second paragraph)". An ordinary practitioner would have been motivated to combine and substitute the method, wherein

the contacting is performed in a system comprising (I) a channel whose surface is coated with a compound that specifically interacts with the chemical moiety, wherein the channel comprises a plurality of ends, (ii) a plurality of wells each suitable for holding a sample, (iii) a connection between each end of the channel and a well, and (iv) a means for moving the sample through the channel between wells of Liu et al in the method of claims 1-22 of U.S. Patent No. 6,046,005 in view of Arbo et al, in order to achieve the express advantages, as noted by Liu et al., of the microtiter well plate format in automated analysis and the potentially low cost of plastic devices, and disposable device equipped with an independent electrospray exit port for each sample well, which represents an attractive alternative to FIA, and also of a device design, which demonstrates the potential of automated analysis.

2. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321© may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground

provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 74-92 are rejected under 35 U.S.C. 103 (a) as being anticipated by Ju et al. (U.S. Patent 6,046,005) (April 4, 2000) in view of Arbo et al. (International Journal of Peptide and Protein Research, (1993), Vol. 42, pages 138-154) further in view of Liu et al. (Anal. Chem. (2000), Vol. 72, pages 33030-3310).

Ju et al teach a method for sequencing DNA by detecting the identity of a single or plurality of dideoxynucleotide incorporated to the 3' end of a DNA sequencing fragment using mass spectrometry (Abstract and Claims 1, 14, and 15, Figure 1 and Experimental Section), which comprises:

a) attaching a chemical moiety via a linker to a dideoxynucleotide to produce a labeled dideoxynucleotide (Claims 1 and 15) ;

b) terminating a DNA sequencing reaction with the labeled dideoxynucleotide to generate a labeled DNA sequencing fragment having a 3' end and the chemical moiety is attached via the linker to the 3' end of the DNA sequencing fragment (Claims 1 and 15 and Figure 1);

c) capturing the labeled DNA sequencing fragment on a surface coated with a compound that specifically interacts with the chemical moiety attached via the linker to the DNA sequencing fragment, thereby capturing the DNA sequencing fragment (Claims 1 and 15);

d) washing the surface to remove any non-bound component (Claims 1 and 15 and Experimental Section);

e) freeing the DNA sequencing fragment from the surface by disrupting and cleaving the interaction between the chemical moiety attached via the linker to the DNA sequencing fragment

and the compound on the surface (Claims 1 and 15 and Experimental Section and Figures 9-10); and

f) analyzing the DNA sequencing fragment using mass spectrometry so as to sequence the DNA (Claim 14).

Ju et al teach a method, wherein the interaction between the chemical moiety attached via the linker to the DNA sequencing fragment and the compound on the surface comprises a biotin-streptavidin interaction (Claims 19-20 and Experimental Section).

Ju et al teach a method, wherein the dideoxynucleotide comprises a cytosine or thymine with a 5-position and the linker is attached to the 5-position of cytosine or thymine (Figure 8 and Experimental Section).

Ju et al teach a method, wherein a plurality of different linkers is used to increase mass separation between different labeled DNA sequencing fragments and thereby increase mass spectrometry resolution (Column 7, lines 1-9 and column 9, lines 15-32).

Ju et al teach a method, wherein the interaction of the linker is cleaved by ultraviolet light (Figures 9-10).

Ju et al teach a method, wherein the chemical moiety comprises biotin, the labeled dideoxynucleotide is a biotinylated dideoxynucleotide, and the surface is a steptavidin-coated magnetic bead solid surface (Figure 1 and Experimental Section and Claim 20).

Ju et al teach a method, wherein the biotinylated dideoxynucleotide is selected from ddATP-11-biotin, ddCTP-11-biotin, ddGTP-11-biotin, ddTTP-11-biotin and the compounds of claims 67-70 (Column 6, lines 35-64 and Figures 8-10).

Ju et al teach a method, wherein the steps (b) to (e) are performed in a plurality of connected containers (Experimental Section).

Ju et al teach method, wherein any linker comprises a photo or chemically cleavable moiety.

Ju et al do not teach method, wherein the cleavable linkers are a derivative of 4-aminomethyl benzoic acid containing fluorine of claim 74.

Arbo et al teach method, wherein the cleavable linkers are a derivative of 4-aminomethyl benzoic acid containing fluorine of claim 74 (Abstract and page 149, Column 2 to page 151, Column 1).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the chemically equivalent cleavable linkers, which are a derivative of 4-aminomethyl benzoic acid containing fluorine of Arbo et al in the method of Ju et al., since Ju et al state, "In such linkers, the linker will comprise a cleavable moiety that is either photo or chemically cleavable (Column 7, lines 1-3)." By employing scientific reasoning, an ordinary practitioner would have been motivated to combine and substitute the chemically equivalent cleavable linkers, which are a derivative of 4-aminomethyl benzoic acid containing fluorine of Arbo et al in the method of Ju et al., in order to achieve the express

advantages, as noted by Ju et al., of linkers which will comprise a cleavable moiety that is either photo or chemically cleavable.

Ju et al. in view of Arbo et al do not teach the method, wherein the contacting is performed in a system comprising (I) a channel whose surface is coated with a compound that specifically interacts with the chemical moiety, wherein the channel comprises a plurality of ends, (ii) a plurality of wells each suitable for holding a sample, (iii) a connection between each end of the channel and a well, and (iv) a means for moving the sample through the channel between wells.

Liu et al. teaches the method, wherein the contacting is performed in a system comprising (I) a channel whose surface is coated with a compound that specifically interacts with the chemical moiety, wherein the channel comprises a plurality of ends, (ii) a plurality of wells each suitable for holding a sample, (iii) a connection between each end of the channel and a well, and (iv) a means for moving the sample through the channel between wells (Abstract and Figures 1-3 and Experimental Section).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the method, wherein the contacting is performed in a system comprising (I) a channel whose surface is coated with a compound that specifically interacts with the chemical moiety, wherein the channel comprises a plurality of ends, (ii) a plurality of wells each suitable for holding a sample, (iii) a connection between each end of the channel and a well, and (iv) a means for moving the sample through the channel between wells

of Liu et al in the method of Ju et al. in view of Arbo et al., since Liu et al. states, "Considering the wide acceptance of the microtiter well plate format in automated analysis and the potentially low cost of plastic devices, a disposable device equipped with an independent electrospray exit port for each sample well represents an attractive alternative to FIA (Page 3304, Column 1, lines 6-10)." Liu et al provides further motivation as Liu et al. states, "Nevertheless, the model application demonstrates the potential of automated analysis with the present device design (Page 3309, Column 1, last sentence of the second paragraph)". An ordinary practitioner would have been motivated to combine and substitute the method, wherein the contacting is performed in a system comprising (I) a channel whose surface is coated with a compound that specifically interacts with the chemical moiety, wherein the channel comprises a plurality of ends, (ii) a plurality of wells each suitable for holding a sample, (iii) a connection between each end of the channel and a well, and (iv) a means for moving the sample through the channel between wells of Liu et al in the method of Ju et al. in view of Arbo et al, in order to achieve the express advantages, as noted by Liu et al., of the microtiter well plate format in automated analysis and the potentially low cost of plastic devices, and disposable device equipped with an independent electrospray exit port for each sample well, which represents an attractive alternative to FIA, and also of a device design, which demonstrates the potential of automated analysis.

Response to Arguments

5. Applicant's arguments with respect to all pending claims have been considered but are they are not persuasive.

Applicant argues (page 4, third paragraph to page 5, line 3) that obviousness type double patenting rejection should be withdrawn because Arbo et al reference does not teach a linker which is a derivative of 4-aminomethyl benzoic acid containing fluorine and the linker taught by Arbo reference is a "very weak coordinating anion". This argument is not persuasive for two reasons. First, the "comprising" language of claim 74 permits any additional step(s) or material(s) to be added in any order with the claimed method. Although the chemical moiety disclosed by Arbo is a TFMSA (trifluoromethane sulfonic acid) associated with non-fluorine containing 4-aminomethyl benzoic acid-based molecule, it meets the claim language because it "comprises" both the 4-aminomethyl benzoic acid and fluorine moieties. Second, in response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., not "very weak coordinating anion" or "very strong coordinating anion") are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicant also argues (page 5, second paragraph) that Liu et al does not teach a channel whose surface is coated with a compound that specifically interacts with a chemical moiety, nor does it teach a channel connected to a well at each end and step (e) of claim 74. This argument is

not persuasive. Liu et al clearly teaches a channel whose surface is coated with a compound (Acrylic-polyester based Casolite AP and Epofix resins in this case) that specifically interacts with a chemical moiety well known in the art, and also teaches a channel connected to a well at each end (Figure 2 and page 3305, column 1). Regarding no teaching of step (e) of claim 74, it was clearly mentioned in the previous office action that Ju et al teaches e) freeing the DNA sequencing fragment from the surface by disrupting and cleaving the interaction between the chemical moiety attached via the linker to the DNA sequencing fragment and the compound on the surface (Claims 1 and 15 and Experimental Section and Figures 9-10).

Applicant then argues (page 10, second paragraph) that 103(a) rejection should be withdrawn because the examiner must demonstrate three things with respect to each claim. First, the cited reference must teach or suggest every element of the claim; second, there should be enough motivation to combine the references; and third, there would have been a reasonable expectation of success. This argument is not persuasive. First, in response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). It has been clearly demonstrated in the response to argument as described above and in the last office action that every element of the claims has been either taught or suggested by the cited references. Second, clear motivation has been provided by Liu et al since Liu et al. states, "Considering the wide acceptance of the microtiter well plate format in

automated analysis and the potentially low cost of plastic devices, a disposable device equipped with an independent electrospray exit port for each sample well represents an attractive alternative to FIA (Page 3304, Column 1, lines 6-10)." Liu et al provides further motivation as Liu et al. states, "Nevertheless, the model application demonstrates the potential of automated analysis with the present device design (Page 3309, Column 1, last sentence of the second paragraph)". Similar strong motivations have been provided by other references as well. Third, with regard to lack of "reasonable expectation of success" argument, there is no evidence of record submitted by applicant demonstrating the absence of a reasonable expectation of success. There is evidence in the Ju reference of the enabling methodology, the suggestion to modify the prior art, and evidence that Ju et al teach a method for sequencing several DNA by detecting the identity of a single or plurality of dideoxynucleotide incorporated to the 3' end of a DNA sequencing fragment using mass spectrometry (Abstract and Claims 1, 14, and 15, Figure 1 and Experimental Section) This evidence of functionality trumps the attorney arguments, which argues that Ju reference is an invitation to research, since Ju steps beyond research and shows the functional product.

Applicant then argues (page 10, third paragraph) that 103(a) rejection should be withdrawn because of the same reasons as set forth in connection with the obviousness-type double patenting rejection. This argument is not persuasive because of the same response to argument as set forth in connection with the maintaining of obviousness-type double patenting rejection.

Conclusion

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CAR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CAR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arun Chakrabarti, Ph.D., whose telephone number is (703) 306-5818. The examiner can normally be reached on 7:00 AM-4:30 PM from Monday to Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703) 308-1119. The fax phone number for this Group is (703) 746-4979.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group analyst Chantae Dessau whose telephone number is (703) 605-1237.

Arun Chakrabarti,

Patent Examiner,

June 25, 2003

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